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# High-dose spironolactone changes renin and aldosterone levels in acutely decompensated heart failure

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ABSTRACT

*Background:* In acutely decompensated heart failure (ADHF) patients with higher aldosterone levels correlate with worse postdischarge outcomes, suggesting that further modulation of the mineralocorticoid system during or immediately after hospitalization might favorably improve outcomes.

*Methods and results:* This was an observational, retrospective secondary analysis of a study including 100 patients with ADHF. In that study 50 patients were submitted to spironolactone treatment (50–100 mg/day). A higher proportion of patients with renin levels above 16.5 pg/mL and aldosterone levels above 100 ng/dL were observed in subjects submitted to spironolactone treatment (44.7% vs. 66.7% and 56% vs. 64.7%, respectively, both $p < 0.05$). In the group of patients submitted to spironolactone treatment the proportion of patients with renin and aldosterone levels above the cutoff had a significant increase from baseline to day 3 (24–32% and 16–44%, respectively, both $p < 0.05$). Log renin and aldosterone were higher in patients with renin and aldosterone levels above the cutoff point (both $p < 0.05$).

*Conclusions:* High-dose spironolactone added to standard ADHF therapy induces an additional increase in renin and aldosterone levels. Whether higher levels of renin and aldosterone due to the reactive response to full MRA still have prognostic value requires further investigation.



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## Introduction

The use of mineralocorticoid receptor antagonists (MRAs) has demonstrated to improve outcomes and reduce mortality in chronic heart failure (HF) and postmyocardial infarction [1–3]. The benefit observed with MRAs is probably due to the excessive neurohormonal activation blockade.

Particularly, aldosterone is probably essential for the progression of HF. Higher aldosterone levels were found in patients with chronic HF when compared with controls, and were found to be associated with poor outcome [4–7]. A rise in aldosterone levels was also observed in the acute myocardial infarction setting [8,9], and likewise associated with worse outcomes in this setting [10].

In acutely decompensated heart failure (ADHF) patients with ejection fraction (EF) <40%, higher aldosterone levels correlate with worse postdischarge outcomes [11], suggesting that further modulation of the mineralocorticoid system during or immediately after hospitalization might favorably improve outcomes. Regarding this matter, high dose spironolactone as add-on therapy in the acutely decompensated heart failure (ADHF) setting has been demonstrated to be safe and likely to provide greater symptomatic relief translated into a more pronounced decrease in natriuretic peptides [12].

We used an ADHF model to study the influence of the MRA spironolactone on renin and aldosterone. The aim of this study is to demonstrate the renin and aldosterone associations and changes before and after the spironolactone introduction.

## Methods

### *Study design*

This study is based on analyzed data from a previous prospective, interventional, clinical trial that we performed [12]. In that study we enrolled 100 consecutive patients who presented in a Portuguese tertiary hospital with ADHF, between February 2012 and February 2013. They were nonrandomly assigned in a sequential 1:1 ratio to spironolactone plus standard ADHF therapy or standard ADHF therapy alone, 50 patients within each arm (i.e. patients were alternatively assigned to spironolactone arm or standard ADHF therapy arm in a sequential manner – the first patient to one arm and the next patient to the other arm. This sequence was repeated until we reach 100 patients, 50 patients within spironolactone group and 50 patients within control group. Patients were blinded to the allocation, and the clinicians were not blinded to the allocation. The recommended spironolactone dose was 100 mg/day; however, the assistant physician could decrease the spironolactone dose to 50 mg/day after 48 h upon admission. After 72 h the study was open label. Furosemide dose and form of administration were performed according to the treating physician.

Patients were eligible for enrollment if they presented with decompensation of chronic HF with symptoms leading to hospitalization. All patients presented at the emergency department severely symptomatic in NYHA class IV. ADHF was diagnosed on the basis of the presence of history of chronic HF, at least one symptom (dyspnea, orthopnea, or edema), one sign (rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography) and elevated natriuretic peptides. Exclusion criteria were: chronic use of MRAs, cardiac surgery within 60 days of enrollment, cardiac mechanical support, cardiac resynchronization therapy within the last 60 days, comorbid conditions with an expected survival of less than 6 months, acute MI at time of hospitalization, hemodynamically significant uncorrected primary cardiac valvular disease, patients requiring intravenous vasodilators or inotropic agents, supine systolic arterial blood pressure <90 mmHg, plasma creatinine (pCr) level >1.5 mg/dL, serum potassium level >5.0 mmol/L, hemoglobin (HgB) level <9 g/dL, and sepsis.

Institutional review board or ethics committee approval was obtained. All the patients provided written informed consent to participate in the study.

### *Study assessments*

Patient's clinical status including physical examination was prospectively recorded by the same assistant physician at day 1 and day 3.

Medications and respective dosages were prospectively recorded by the investigators according to the assistant physician prescriptions.

Blood and spot urine samples were collected in the first 24 hours (h) after admission (day 1) of the patient to the hospital. The first dose of spironolactone was only administered after the first sample was collected. Fifty patients had daily oral spironolactone according to the study protocol described above. The day 3 samples were collected between 72 and 96 h of hospitalization. All the samples were collected in the morning with the patient in supine position, and first-morning spot urine was used. All the patients had low-salt, low-calorie hospital diet. Extra fruit and vegetables administration was not allowed. An assessment of biomarkers (including pCr, plasma urea [pUr], electrolytes, N-terminal pro-brain natriuretic peptide [NTproBNP], high-sensitivity troponin T [hsTnT], and proteinuria) was performed at a central core laboratory at day 1 and day 3. Clinical assessment and routine analyses were performed daily during hospital stay. A transthoracic echocardiography was performed on all the patients within 72 h upon admission. Left ventricle ejection fraction (LVEF) was calculated according to the biplane Simpson method.

Aldosterone was measured using radioimmunoassay (RIA) Coat-a-Count® (Siemens) and renin with RIA (DiaSource®).

### *Variable definitions*

We defined high renin levels when values were above the 16.5 pg/mL cutoff, and high aldosterone levels when values were above the 100 ng/dL cutoff. The manufacturer suggested a cutoff of 16.5 pg/mL for renin and a cutoff of 160 ng/dL for aldosterone. We lowered aldosterone cutoff to 100 ng/dL to increase test sensitivity, although levels above 160 ng/dL are more specific, we might miss important information, since